On tumor development: fractional transport approach

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A growth of malignant neoplasm is considered as a fractional transport approach. We suggested that the main process of the tumor development through a lymphatic net is fractional transport of cells. In the framework of this fractional kinetics we were able to show that the mean size of main growth is due to subdiffusion, while the appearance of metaphases is determined by superdiffusion.

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I. INTRODUCTION

Application of fractional calculus in biology is mainly used to describe an activity of living system(see recent reviews [1]). Our purpose is to describe a tumor growth process by means of cell transport inside a fractional network. In the present consideration we propose a link between tumor spread and fractional transport, whose mathematical apparatus is well established [2, 3, 4] We propose simplified mathematical models using heuristic arguments on tumor growth. On the basis of statement, we are citing [5]: "Lymphatic spread is more typical of carcinomas whereas the hematogenous route is favored by sarcomas. There are numerous interconnections, however, between the lymphatic and vascular systems, and so all forms of cancer may disseminate through either or both systems." - we focus on a possible mechanism of this growth as a result of fractional transport of cancer cells along lymphatic net system, which has a fractal Hausdorff dimension [1]. Using a simplified approach of fractional transport, we are also suggesting a possible answer on a question how neoplasm cells appear arbitrary far from a main tumor. The tumor growth is a complicated process which consists of consequences of various and different phases. This phases can be considered as independent processes with different time duration. The last depends on various environmental conditions as well.

The growth of malignant neoplasm can be described as a two-step process [5]. The first phase is the growth and differentiation of the primary tumor and the second phase can be described as a metastatic phase, during which there are many changes in the primary tumor's cells that lead to the metastasis. The difference between the methastatic cells and the cells of the primary tumor includes, for example, a different expression of adhesion molecules such as E-cadherins, catenins etc. [6]. Those differences are discussed in many studies, see e.g. [7], according to which after certain proliferation of the primary tumor the metastatic stage begins - the cells start to express different molecules. Those cells separate from the primary tumor - a process is named metastasis.

The metastasis cells can be spread throughout the lymphatic net system or throughout the blood stream (vascular system) [5]. Apparently, there are cytokines which support the lymphatic proliferation and encourage the directional movement toward lymphatic system [8]. There are tumors which express different specific chemokine receptors and they are more likely to spread through the lymphatic system.

In the present paper we suggest a simplified scheme of tumor spread along the lymphatic net. In our scheme we are introducing two - step process, where the first one is a biological process of cells fission. The second phase is cells transport itself inside lymphatic net structure. We primary focus on the second phase, supposing that the main size of the tumor development is due to fractional transport, and present the two times tumor development model (TTT-model).

II. MAIN ASSUMPTIONS FOR THE TWO TIMES TUMOR DEVELOPMENT MODEL

In order to construct the TTT-model for the tumor development description we are introducing a number of assumptions which are essential for our approach:
(a) We suppose, that there are two time scales $\mathcal{T}_f$ and $\mathcal{T}_t$. The first one corresponds to the volume grow due to proliferation of cells by fission. During this time cells are strongly interacted [9]. There is no cell transport, and only the fed cells can proliferate. The duration of $\mathcal{T}_f$ could be arbitrary large and it can reach $10^7 - 10^8 sec$ [5]. The second time $\mathcal{T}_t$ corresponds to cell transport. We suppose that during this time there are enough cells without fission, and the interaction between tumor cells is rather small. Hence the cells form an initial packet of free particles, which spread along the lymphatic net.
(b) The lymphatic net is a system of organic tubes with complicated crosses and arbitrary (random) number of entrances at nodes. It fulfilled by lymphatic liquid with laminar flow. Citing [5, 10] "About 100 milliliters per our of lymph flows through the thoratic duct of a resting human and approximately another 20 milliliters flows into

the circulation each hour through other channels, making a total estimated lymph flow of about $120ml/hr$, that is between 2 and 3 liters per day". The Hausdorff dimension of this geometry is fractal $d_f < 3$ (3 is embedding dimension). Since the geometrical dimension of the lymphatic net is fractional, the neoplasm development corresponds to anomalous diffusion.

(c) The tumor spreading process consists of the following time consequences

$$\mathcal{T}_f(1)\mathcal{T}_t(2)\mathcal{T}_f(3)\dots. \tag{1}$$

There are different realizations of this chain of times, due to different duration of $\mathcal{T}_f(i)$ and $\mathcal{T}_t(i)$, where $i = 1, 2, \dots$ and it means simply a step–number of the process. It should be underlined that the processes with different steps i are absolutely independent and there is possible any realization of the time duration $\mathcal{T}_t(i)$. Therefore, one can introduce the probability distribution function (PDF) for $\mathcal{T}_t(i)$. As a result of these realizations, there are few scenarios of the tumor development. This process depends on the rate of the tumor cell spreading. If transport is subdiffusive, that is typical for the lymphatic spread of carcinomas [5], it can be described in the framework of continuous time random walk (CTRW) [4, 12]. The transport can be superdiffusive due to so-called Levy-type flights when cells may traverse all of the lymph nodes ultimately to reach the vascular compartment via the thoratic duct. In this case for any anatomic localizations metastasis are possible. It should be stressed that an every cell (a particle) carries with itself its own trap, and this is the principal deference from the standard CTRW, where traps are external with respect to the transporting particles.

III. SUBDIFFUSIVE GROWTH

There are many possibilities to describe the cell transport as a diffusive process taking place during the time scales $\mathcal{T}_t(i)$ in the framework of the fractional calculus. One of the simplest approximation for this process is CTRW. We used here a simplified model which neglects proliferation of cells. It means that a number of cells participated in the transport is conserved. Suppose that $\mathcal{T}_f(i) \gg \mathcal{T}_t(i)$, and following the CTRW construction (see, for example, [4]), we believe that during $\mathcal{T}_t(i)$ a cell "jumps" with the jump length variance

$$\sigma^2 = \int_{-\infty}^{\infty} l^2 \psi(l,t) dl dt \tag{2}$$

and $\mathcal{T}_f(i)$ are waiting times elapsing between two successive jumps, where

$$\mathcal{T} = \int_0^{\infty} t\psi(l,t) dl dt \tag{3}$$

is the mean waiting time. These values are characterized by a probability distribution function (PDF) $\psi(l,t)$. If the waiting time distribution has the following form

$$\tilde{\psi}(t) = \int_0^{\infty} \psi(l,t) dl \sim 1/(1 + t/\mathcal{T})^{1+\alpha}, \tag{4}$$

with $0 < \alpha < 1$ the behavior for a CTRW is subdiffusive with the mean squared displacement being

$$\langle l^2(t) \rangle \sim t^{\alpha}. \tag{5}$$

This subdiffusive relaxation process is responsible for the size of the primary tumor. It may be relevant if one takes into account that during times $\mathcal{T}_t(i)$ there is diffusion on fractal lymphatic net of dimension d_f. The mean squared displacement in this case is given by (5), where the transport exponent α depends now on d_f. In these cases the relaxation process is modeled by fractional diffusion equation, where the PDF $\psi(l,t)$ has non-Gaussian form. The square root from mean squared displacement $\langle l^2 \rangle$ is an average size of the main tumor development.

When $\alpha > 1$, the transport on the fractal lymphatic net is superdiffusive. It may describe a metastasis process. In this case $\sqrt{\langle l^2(t) \rangle}$ is an average distance between a new tumor location and the primary tumor after time t. This time $t \sim \mathcal{T}$ is a time when a cell moves long enough without fission.

IV. COMB MODEL

In what follows we consider a simple model of fractional transport of neoplasm cells. In the framework of this model we are able to determine the size of the tumor development. Anomalous diffusion on a comb model is an oversimplified presentation of diffusion on the fractal lymphatic net. The model was proposed in [13] for drift particles in percolation systems and used for some applications in solid state [14] and biophysics [15]. The comb–like geometry shown in Fig. 1 is a toy model of a porous diffusion medium. We borrow this consideration from [14] primary to describe subdiffusion of cancer cells on the lymphatic net and demonstrate a fractal nature of cancer cells transport as well as to determine a size of cancer growth. A special feature of diffusion in this model is a possibility of motion in the x-direction only along the structure axis, when $y = 0$. In this case motion in the y–direction is a trap, where a particle stays in the comb teeth for some time before it moves along the structure x–axis. This model approximates cell transport along the lymphatic net embedded in 3D sphere (R, θ, ϕ). Diffusion along the structure axis (y=0) specifies motion along the lymphatic net leading to the increasing of the radial size $R = R(t)$ of the tumor. Motion along the y-direction corresponds to cell transport in the polar and azimuthal directions. This motion does not lead to the increase of the radial size of the tumor and may be considered as a trap. The PDF of waiting or delay times for the infinite teeth is $\psi(t) \sim t^{-\beta}$, where $1 < \beta < 2$, such that the mean waiting time is diverged. It follows from the presented

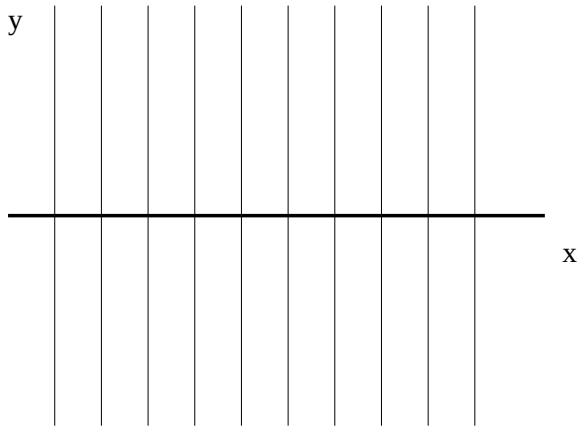

FIG. 1: The comb structure

geometry, that the diffusion coefficient D_{xx} differs from zero only when $y = 0$, namely $D_{xx} = D_1\delta(y)$. The diffusion coefficient along the y direction is $D_{yy} = D_2$ and $D_{xy} = D_{yx} = 0$. Therefore, The Fokker–Planck (FP) equation for the Green function $G \equiv G(x, y, t)$ reads [14]

$$\frac{\partial G}{\partial t} - D_1\delta(y)\frac{\partial^2 G}{\partial x^2} - D_2\frac{\partial^2 G}{\partial y^2} = \delta(x)\delta(y)\delta(t)\,. \qquad (6)$$

In the Laplace–Fourier (p, k) space after carrying out corresponding transformations for the x, t variables we obtain from Eq. (6) the following solution [14]

$$G(k, y, p) = \frac{\exp\left[-(p/D_2)^{1/2}|y|\right]}{2(D_2p)^{1/2} + D_1k^2}\,. \qquad (7)$$

For diffusion along the structure axis one can infer the Green function $c(x, t) = G(x, 0, t)$ [14]. Therefore, the mean squared displacement of mobile particles is anomalous subdiffusion:

$$\langle x^2(t)\rangle = \frac{\langle x^2(t)c(x,t)\rangle}{\langle c(x,t)\rangle} = D_1(\pi t/D_2)^{1/2}\,. \qquad (8)$$

This mean squared displacement $\langle x^2(t)\rangle$ is a mean radial size of the tumor after elapsing transport time t. For the TTT model it means that a general elapsed time is

$$t \equiv t_N = \sum_{i=1}^{N}(\mathcal{T}_f(i) + \mathcal{T}_t(i)) = t_f + t_t. \qquad (9)$$

During the fission time t_f neoplasm cells do not move, then $t = t_t$ in (8). If t_t is large enough, this process may give a possible explanation not only for the mean size of the primary tumor but also it could be mean distance between the primary tumor and a metastasis.

The transport (or grow) process accelerated by including so-called Lévy–type flights into consideration. In the framework of the comb model it still leads to subdiffusion with transport exponent $1/2 < \alpha \leq 1$ [16]. Therefore to obtain a superdiffusion process one needs to go beyond the comb model consideration. The transport can be superdiffusive due to Levy-type flights when cells may traverse all of the lymph nodes ultimately to reach the vascular compartment via the thoratic duct. In this case the Levy–type process is a result of the cell transport in the vascular system. Therefore, the solution of Eq. (7) should be modified in the following way: along the structure axis we add Lévy flights with a Lévy distribution for the jump length with the asymptotic behavior [4]

$$\tilde{\psi}(x) \sim |x|^{-1-\mu}\,, \qquad (10)$$

where $1 < \mu < 2$. The solution Eq. (7) is modified, for example, in the following form [17]

$$G_L(k, 0, p) = \frac{1}{D_2p^{1/2} + D_1|k|^{\mu}}\,. \qquad (11)$$

The power–law asymptotics for the Green function is

$$c(x, t) \sim \frac{t^{-g_\mu}}{|x|^{1+\mu}} \qquad (12)$$

with $g_\mu > 0$. For example, when $\mu = 1$, $g_\mu = 1$. In this case the mean squared displacement diverges:

$$\langle x^2(t)\rangle \longrightarrow \infty\,. \qquad (13)$$

This expression of Eq. (13) could be a simple explanation of appearance of metaphases at any long distance from the primary tumor.

V. CONCLUSION

A cancer growth process is considered in the framework of the TTT model. It is shown that the main process of the tumor development is a fractional transport of cancer cells on the lymphatic net. In the framework of this fractional kinetics we were able to show that the mean size of the main growth is due to subdiffusion, while the appearance of metaphases is determined by superdiffusion. The underlying mechanism of the tumor development is a partition of this grow on fission times $\mathcal{T}_f(i)$ and transport times $\mathcal{T}_t(i)$. Due to this assumption, there are free cancer cells, which contributes to fractional transport. Therefore, both the characteristic size of the cancer growth and metaphases are related to the fractional transport exponents α, μ, which depends on geometrical fractional dimension of the lymphatic net d_f.

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